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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/776,910	02/06/2001	Robyn Joyce Russell	50179-087	3696

7590 05/19/2004

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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/776,910	RUSSELL ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 23 April 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ they raise the issue of new matter (see Note below);
   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.
3. ☐ Applicant's reply has overcome the following rejection(s): _____.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See attached*.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *9 and 14-18*.

   Claim(s) withdrawn from consideration: *10-12, 19-29*.
8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.
10. ☐ Other: _____

Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit: 1652

Advisory Action

Claims 9-12, 14-29 are still pending in this application. Claims 9, 14-18 are now under consideration. Claims 10-12, 19-29 remain withdrawn from consideration as being drawn to non-elected invention.

The amendment filed on 4-23-04 in response to the final rejection has been considered and ENTERED but does not place the application in condition for allowance because of the following.

While applicant's amendment and arguments does overcome the previous objections and rejections under 35 U.S.C. 112, 2nd paragraph, they are not persuasive to overcome the rejections under 35 U.S.C. 112, Ist paragraph and 35 U.S.C. 102(b).

Examiner continues to maintain that claims 9, 13-17 while being enabling for an enzyme with SEQ ID NO:8, 10 or 13 and encoded by either SEQ ID NO:1, 3, 5, 7 and having a amino acid substitution at position 251, wherein the substituted amino acids are either Leu, Ser, Ala, Ile, Val, Thr, Cys, Met or Gly and capable of hydrolyzing organophosphates, does not reasonably provide enablement for any such enzyme encoded by a polynucleotide that is either 80% or 95% homologous to SEQ ID NO:7 or any such enzyme having at least 75% homology to SEQ ID NO:8 and differing from SEQ ID NO:8 in having a amino acid substitution at position 251, wherein the substituted amino acids are either Leu, Ser, Ala, Ile, Val, Thr, Cys, Met or Gly. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. (See previous Office action)

Applicants argue that the rejection under 35 U.S.C. §112, first paragraph is not proper and that Examiner has confused the claimed polypeptide sequence (SEQ IDNO:8) and clarify that the instant claims are directed to recombinant *L.cuprina* sequence (SEQ ID NO:8) and sequences sharing 75% similarity thereto which exhibit organophosphate resistance. Applicants argue that claims are directed to a specific sequence with a specific structure and that the specification shows, through sequence alignments, that the claimed polypeptide can tolerate up to at least 25% sequence variation and that the sequence alignments provided demonstrate this fact. Therefore, applicants argue, that one skilled in the art would know how to make substitutions in the amino acid sequence of SEQ ID NO:8. Examiner respectfully disagrees with such an argument to be persuasive to overcome the above rejection. Examiner acknowledges that applicants provide the sequence alignment of SEQ ID NO:8 with that of SEQ ID NO:13 in figure 2. However, it should be noted that it is SEQ ID NO:8 that has 75% sequence identity to SEQ ID NO:13 and not the other way round. Applicants are claiming a polypeptide that is 75% identical to SEQ ID NO:8 which is already 75% identical to SEQ ID NO:13. Therefore while those skilled in the art would probably know how to make changes to SEQ ID NO:13, using the above alignment, they would not know how to make further changes to a polypeptide that is already different from the reference molecule, i.e., SEQ ID NO:13. Applicants arguments would hold water if they were claiming amino acid sequence that is 75% identical to SEQ ID NO13, because they do provide a polypeptide that can tolerate 25% amino acid changes and such a polypeptide is SEQ ID NO:8. The specification lacks any teaching or guidance as to how those skilled in the art would be able to make further changes to SEQ ID NO:8 without any undue experimentation.

In view of the above, applicant's arguments are not persuasive because while methods to produce variants of a known sequence, such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants as claimed by applicants requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the large number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein (i.e. structure of SEQ ID NO:8) and polynucleotides (SEQ ID NO:7)which may be modified without effecting activity; (B) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (C) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Hence the above rejection is maintained.

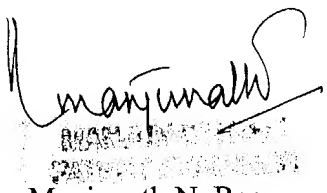
Examiner also continues to maintain the rejection of claims 9, 13-18 under 35 U.S.C. 102(b) as being anticipated by Whyard (a) et al. (Pesticide Biochemistry and Physiology, 1994, Vol. 50(3):198-206) or Whyard (b)et al. (Biochemical genetics, 1994, Vol. 32(1-2):9-24). See previous Office action

In response to the above rejection , applicants argue that the enzyme in the reference is not the same as that claimed. First of all it should be noted that applicants base their arguments

using information that is outside the specification, and that too a publication that is post dated to the date of filing of the instant application. Applicants argue that the K_m and K_{cat} of the isolated enzyme in the reference is different from that of the instantly claimed enzyme and therefore the claimed recombinant enzyme is different from that the isolated enzyme in the reference. Next applicants argue that the reference concludes that the malathion resistance and susceptibility between the two strains is due to a "quantitative rather than a qualitative change in the MCE of the two strains" which is in contrast to the disclosure in the instant specification that the difference is due to a qualitative difference. Finally applicants also argue that the reference reports that the enzyme is found in mitochondria in contrast to the applicants "advise" (applicants make no reference to the presence of such information in the specification) that the enzyme does not have a mitochondrial targeting signal and therefore there is no evidence to that effect. Therefore, applicants claim that there are three differences between the reference enzyme and the instant claimed enzyme and hence the reference does not anticipate instant claims. Examiner respectfully disagrees with such an argument. As stated earlier, applicants are basing their arguments from information gained from a post dated research paper and an "advise" that is outside the specification. Applicants have not shown that they have support for all the above differences in their specification. Therefore, Examiner continues to maintain that the above reference anticipates claims 9 and 13-18 as written and filed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The examiner can normally be reached on 6.30 a.m. to 3.00 p.m. If attempts to reach the

examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao
May 14, 2004